Weekly Paclitaxel Combined with Monthly Carboplatin in Elderly Patients with Advanced Non-small Cell Lung Cancer: A Multicenter Phase II Study

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Introduction: We designed this phase II trial to evaluate the efficacy and safety of weekly paclitaxel in combination with monthly carboplatin as first-line treatment in elderly patients with advanced non-small cell lung cancer (NSCLC).

Methods: Main eligibility criteria were histologically or cytologically proven stage IIIB or IV NSCLC, age ≥70 years, Eastern Cooperative Oncology Group performance status 0-2, and measurable disease. The 4-week–based chemotherapy regimen consisted of carboplatin infusion (area under the concentration-time curve 6 $mg/ml^{-1}/min$) on day 1 and paclitaxel 90 mg/m^2 as a 1-hour infusion on days 1, 8, and 15. Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors criteria, and symptoms were evaluated using the Lung Cancer Symptoms Scale. Analyses were performed on an intention-to-treat basis.

Results: From February 2002 to August 2003, 51 patients (median age, 74 years) participated in the study. One complete and 21 partial responses were reported by the independent review committee, leading to an intention-to-treat objective response rate of 43% (95% confidence interval, 30–57%). The median progression-free and overall survivals were 7.5 (95% confidence interval, 6.2–9.4) and 13.6 (95% confidence interval, 7.5–17) months, respectively. Longitudinal evaluation of the Lung Cancer Symptoms Scale demonstrated lack of quality of life modification during the treatment period. Neurotoxicity was mild to moderate, with 6% of patients suffering from a grade 3 or 4 neuropathy. Myelosuppression was the main toxicity; 39% of patients experienced grade 3 or 4 neutropenia, 18% experienced grade 3 anemia, and 8% experienced grade 3 or 4 thrombocytopenia. There was no treatment-related death.

Conclusions: The combination of weekly paclitaxel 90 mg/m^2 administered on days 1, 8, and 15 plus monthly carboplatin area under the curve 6 on day 1 of a 4-week cycle was feasible and active as a first-line treatment for elderly patients with NSCLC with a good safety profile. These results deserve further analysis to compare the standard care for these patients (monotherapies) with this doublet.

Key Words: Non-small cell lung cancer, Efficacy/safety ratio, Paclitaxel, Carboplatin, Elderly, Phase II, Quality of life.

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Lung cancer is the major cause of cancer-related death in the elderly population. More than one half of patients with lung cancer are older than 60 years at diagnosis, and one third of all patients with non-small cell lung cancer (NSCLC) are older than 70 years.[1] A study of survival among patients with lung cancer in European countries (EUROCARE program) showed 1-year and 5-year overall survival of 28% and 7%, respectively, in patients more than 70 years old.[2] Comorbidities affecting the elderly population and limiting the use of standard treatments could be one of the reasons explaining this low survival rate. Therefore, the development of specific care for this patient population is needed.

Platinum-based combinations have been accepted worldwide as regimens to treat advanced NSCLC because of a clear survival improvement using various platinum-based doublets compared with best supportive care only.[3] However, elderly patients are often unsuitable for cisplatin-based chemotherapy because of the physiological reduction of functional reserves. Some of the more recently developed chemotherapeutic agents are better tolerated than the older cisplatin-based combinations, with favorable therapeutic indices in the elderly. Paclitaxel, the prototypical taxane, induced a 20% response rate in patients with advanced NSCLC[4,5] and has been associated with an improvement in 1-year survival in phase III trials.[6] Even if there is a concern regarding the equivalence in terms of efficacy,[7] the substitution of cisplatin by carboplatin in a doublet regimen offers patients a clear reduction in risk of renal impairment and neurological toxicity when it is administered according to a projected area under the concentration-time curve (AUC).

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When paclitaxel and carboplatin are combined every 3 weeks, response rates among patients with advanced NSCLC ranged from 27% to 41%, median survival ranged from 10 to 12 months, and 1-year survival ranged from 30% to 54% without major toxicity.[8–10] Paclitaxel 200 mg/m^2 and carboplatin AUC 6 mg/ml^{-1}/min given every 21 days as first-line chemotherapy were evaluated retrospectively in elderly patients (aged ≥70 years) with NSCLC and showed a good response rate and acceptable toxicity.[11] However, this report included only a subgroup of a larger study that was not specifically designed for the elderly. No study had been designed to evaluate the carboplatin-paclitaxel doublet in the elderly population.

Weekly exposure to paclitaxel might offer higher antitumor activity compared with the paclitaxel every-3-weeks schedule because it is thought to reduce the chance of resistant cell clone emergence by shortening the intervals between administrations. According to a phase I-II study in NSCLC, weekly paclitaxel is well tolerated and yields a good therapeutic index that compares well with the standard schedule.[12] In a recent randomized phase II study comparing three different schedules of weekly paclitaxel and carboplatin (delivered on either a weekly or monthly schedule), the optimal efficacy/safety profile was observed with the following regimen: paclitaxel 100 mg/m^2 given on days 1, 8, and 15 and carboplatin AUC 6 mg/ml^{-1}/min on day 1 of a 28-day cycle.[13] The acceptable tolerance of this schedule makes it deserving of evaluation among patients with NSCLC with unfavorable conditions at presentation, such as are frequently observed in the elderly.

In this phase II study, we aimed to determine the efficacy and safety of weekly paclitaxel combined with monthly carboplatin as first-line treatment among elderly patients with advanced NSCLC. Paclitaxel was used at the dose of 90 mg/m^2 on days 1, 8, and 15 in combination with carboplatin AUC 6 mg/ml^{-1}/min on day 1 of a 28-day cycle.

PATIENTS AND METHODS

Patient Eligibility

Patients older than 70 years with chemonaive histologically or cytologically proven stage IIIB or IV NSCLC not suitable for surgery were eligible. Patients with stage IIIB were eligible whether their disease was advanced so that radiotherapy could not be given at curative intent. Patients with local or metastatic failure after surgery and/or radiotherapy were eligible for the study if at least one indicator lesion could be measured according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[14] The indicator lesion had to be outside a previously irradiated area. Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) between 0 and 2 and an estimated life expectancy of at least 12 weeks. Patients were required to have adequate bone marrow reserve (neutrophils ≥2/10^9/L, platelets >125/10^9/L) and satisfactory hepatic (bilirubin ≤1.5 times the upper institutional limits of normal [ULN], alanine transferase <2.5 UNL or ≤5 UNL in the presence of hepatic metastases) and renal functions (serum creatinine ≤1.5 UNL and creatinine clearance ≥60 ml/min). In addition, patients had to have recovered from recent surgery and radiation therapy (with at least 1 week elapsed from the time of a minor surgery and at least 3 weeks from major surgery and radiotherapy). Non-eligibility criteria consisted of the presence of symptomatic central nervous system metastases, evidence of any peripheral neuropathy, prior allergic reactions to drugs containing Cremophor (BASF Aktiengesellschaft, Ludwigshafen, Germany), active infection, or prior malignant disease (except well-controlled basal cell skin cancer or in situ cervix carcinoma). Written informed consent was obtained from every patient before study entry. The study was conducted in accordance with good clinical practices and was approved by the local ethics committee.

Treatment Plan

Eligible patients were treated with paclitaxel plus carboplatin for up to six cycles, except in the case of tumor progression, inter-current disease, unacceptable toxicity, or patient's refusal to continue. The 4-week–based chemotherapy regimen consisted of a carboplatin (Paraplatin; Bristol-Myers Squibb, Rueil-Malmaison, France) infusion given on day 1 with AUC 6 mg/ml^{-1}/min as calculated using Calvert's formula, and paclitaxel (Taxol; Bristol-Myers Squibb) 90 mg/m^2 as a 1-hour infusion on days 1, 8, and 15. The following premedications for prophylaxis of hypersensitivity reactions were administered 30 minutes to 1 hour before paclitaxel: (a) dexamethasone 10 mg IV; (b) dexchlopheniramine 5 mg IV; and (c) cimetidine 300 mg IV or ranitine 50 mg IV. A cycle restarted at day 28 pending hematological recovery; i.e., the absolute neutrophil count >1.5/10^9/L and platelets >100/10^9/L, and return to grade 0 or 1 for non-hematological toxicity. If one or more of these conditions was not met, then a 1- to 2-week delay was allowed for recovery. Dose reductions were required for both paclitaxel and carboplatin pending the occurrence of one of the following toxicities: grade 4 neutropenia lasting 7 days or more during the previous cycle; grade 3 or 4 febrile neutropenia; grade 3 or 4 infection with neutropenia; grade 4 anemia or thrombocytopenia or bleeding requiring transfusion; grade 2 neurotoxicity; and any grade ≥3 non-hematological toxicity. Study drugs were discontinued in the case of grade ≥2 hearing disorders or renal toxicity (carboplatin); grade ≥3 hypersensitivity reactions (paclitaxel) and grade ≥ 2 cardiotoxicity; or hepatoxicity and grade ≥ 3 pain or neurotoxicity (both drugs). Paclitaxel was administered on days 8 and 15 depending on hematological recovery; i.e., the absolute neutrophil count >1.5/10^9/L and platelets >100/10^9/L, and return to grade 0 or 1 for non-hematological toxicity.

Study Assessments

Pretreatment evaluation included a complete medical history and clinical examination with tumor measurements (imaging studies and physical examination when appropriate), electrocardiogram, chest radiograph, appropriate radiological tests, concomitant treatments, PS, quality of life (QoL) according to the Lung Cancer Symptoms Scale (LCSS), and hematological and biochemical profiles. Tumor measurements were performed every other cycle during the

study and every 3 months subsequently until progression. LCSS was evaluated at baseline and before each cycle. During the study, complete blood counts including a platelet and leukocyte differential count were performed weekly, and blood chemistry was also analyzed before each cycle.

Response and Toxicity Criteria

Patients were evaluated for response and progression according to the RECIST criteria.[14] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST. A minimal duration of 4 weeks was required to document a response, and the best response was recorded for each patient. Clinical responses were reviewed by independent experts. Time to response was defined as the time from the first dose of study drug until the first objective status assessment of partial/complete response. Response duration was measured from the time measurement criteria for partial/complete response was first registered until the first time that recurrent or progressive disease was objectively documented. Progression-free survival was defined as the time from the date of registration until the date of progression or death. Survival was defined as the time from the date of registration (informed consent date) to the date of death.

Toxicity, graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0), was assessed by clinical examination and biological tests before each cycle of chemotherapy.[15]

Lung Cancer Symptoms Scale

This scale is specifically designed for research and clinical use in lung cancer populations and focuses primarily on the physical dimension, particularly symptoms and symptomatic distress specific to lung cancer and subsequent QoL.[16] It consists of two scales: one completed by the patient (nine items as visual analogue scales from 0 to 100) and one for health care professionals (six items as five-point categorical scales) to provide context. An average of the aggregate score of all nine items was used for a total score for patient scale.

Statistical Considerations

The primary end point of the study was the objective response rate (ORR) of the combination of weekly paclitaxel with monthly carboplatin in elderly patients with NSCLC. A modified Simon optimal two-stage design was used to test whether the ORR was of clinical interest.[17] A minimum of 19 evaluable patients and a maximum of 44 evaluable patients had to be included in the study. Taking into account that a 20% response rate is usually observed in chemotherapies for elderly patients (e.g., single-drug chemotherapy), a response rate of at least 35% was considered of clinical interest. Estimates of median time to response, duration of response, progression-free survival, and overall survival with their 95% confidence intervals (CI) were calculated using the Kaplan-Meier product-limit method. For toxicity analyses, the worst grade for each patient in all cycles of chemotherapy was used. Actual dose intensity for each drug was defined as the ratio of the administered dose per unit of time to the planned dose per unit of time.[18] For each patient, the dose intensity was calculated taking into account the actual time of treatment plus 4 weeks. The relative dose intensity of paclitaxel by patient was calculated as the dose intensity in mg/m^2/week actually received divided by the planned dose intensity. The planned dose intensity was 67.5 mg/m^2/week. The relative dose intensity of carboplatin by patient was calculated as the dose intensity in AUC/week actually received divided by the planned dose intensity in AUC/week. The planned dose intensity was AUC 1.5 mg/ml^{-1}/min/week.

All analyses were performed on an intention-to-treat (ITT) basis. The statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Patients

From February 2002 to March 2003, 51 elderly patients with NSCLC from eight French centers were included in the study. Patients' characteristics at baseline are summarized in Table 1. Most patients were male, and the median age was 74 years (range, 69 to 88 years). One 69-year-old patient was

TABLE 1. Baseline patient characteristics

	Number of patients	(%)
Age (yr)		
Median	74.0	
Range	69–88	
Mean (SD)	75.2 (4.7)	
Sex		
Male	38	75
Female	13	25
ECOG PS		
0	15	29
1	31	61
2	5	10
Histology		
Squamous cell carcinoma	18	35
Adenocarcinoma	27	53
Large cell carcinoma	3	6
Other	3	6
Stage		
IIIB	9	18
IV	42	82
Metastatic sites		
0	8	16
1	25	49
2	15	29
≥4	2	4
Missing	1	2
Prior surgery	13	25
Time from last surgery to informed consent (mo)		
Median	1.3	
Range	0.1–37.8	

n = 51. ECOG, Eastern Cooperative Oncology Group; PS, performance status.

accrued into this study and has been considered a protocol deviation at registration. ECOG PS was 0 or 1 for most patients. Adenocarcinoma and squamous cell carcinoma were the most frequent histologies, and most patients had stage IV disease.

Treatment Exposure

A total of 209 cycles were administered in 51 patients with a median number of four cycles per patient (range, one to six cycles). Overall, 174 cycles (83%) were completed. Paclitaxel was not administered on days 8 and 15 for eight cycles (4%), and on day 15 for 27 cycles (13%). Of 584 infusions, 26 (4%) were delayed because of hematological toxicity (11 infusions), non-hematological toxicity (four infusions), and reasons other than toxicity (patients' or investigators' decision, 10 infusions). Chemotherapy was discontinued early in 33 patients (65%) because of study treatment toxicity (11 patients), disease progression or relapse (nine patients), other reasons including adverse events not related to study drugs (nine patients), patient's request (two patients), and death (two patients). The mean duration of treatment was 3.8 months. Dose intensity was analyzed on an ITT basis. Mean (± SD) relative dose intensity for paclitaxel was 0.85 ± 0.15 and for carboplatin was 0.95 ± 0.07.

Efficacy

Efficacy results based on the ITT population and on reviewed data are summarized in Table 2. One complete (2%) and 21 partial responses (41%) were reported by the expert panel leading to an ORR of 43% (95% CI, 30%–57%). The response rate according to investigators' analyses was congruent, giving an ORR of 41% (95% CI, 28%–55%; 1 complete response and 20 partial responses). The median time to response was 1.87 months, and median progression-free survival was 7.49 months. Panel reviews were not conducted until progression of patients. Therefore, all data were based on panel assessments, except for progression-free survival, which was calculated using investigators' assessments (Figure 1).

TABLE 2. Efficacy results based on reviewed data in the ITT population

		Number of patients	%
Best tumor response			
Complete response		1	2
Partial response		21	41
Stable disease		15	29
Progressive disease		8	16
Unable to determine		5	10
Not evaluated		1	2
Overall best response rate (%)	CR+PR	43	
	95% CI	0.30–0.57	
Time to response (mo)	Median	1.87	
	95% CI	1.84–2.00	
Progression-free survival (mo)	Median	7.49	
	95% CI	6.21–9.43	
Overall survival (mo)	Median	13.63	
	95% CI	7.49–17.05	

n = 51.CI, confidence interval; CR, complete response; PR, partial response.All data are based on panel assessment except for progression-free survival, which was calculated using investigators' assessment.

Symptoms and Quality of Life

Symptoms and QoL changes over time are summarized in Table 3. There was no significant change over time in the total score (as defined by the average of the aggregate score of all nine items).

Safety

The worst NCI-CTC toxicity grades experienced by patients for the laboratory parameters are given in Table 4. Myelosuppression was the most common toxicity. Neutropenia was observed in 76.5% of patients; grade 3 or 4 was observed in 39% of patients. One case of febrile neutropenia was reported. Anemia was experienced by 84.3% of patients; 18% of patients experienced grade 3 anemia. No grade 4 anemia occurred. Thrombocytopenia was observed in 23.5% of patients; grade 3 or 4 toxicity was observed in 8% of patients. No hemorrhagic episode was reported. Abnormalities of hepatic or renal functions were generally mild, reversible, and not clinically relevant. However, one patient had a grade 3 toxicity for creatinine without any clinical consequence (Table 4).

Besides myelosupression, adverse events (AEs) possibly or probably related to study drugs were usually mild in severity and manageable. The most common related AEs occurring during the study were alopecia (57% of patients), fatigue (55%), nausea (41%), vomiting (24%), and constipation (20%). Grade 3 or 4 AEs were uncommon (Table 5) and included grade 3 fatigue in six patients (12%), grade 3 constipation in two patients (4%), and grade 3 anorexia in two patients (4%). Sensitive neuropathy (mainly reported as paresthesia) affected up to 30% of the patients. Three patients experienced grade 3 or 4 neuropathy: two grade 3 and one grade 4. No death related to therapy occurred during the study.

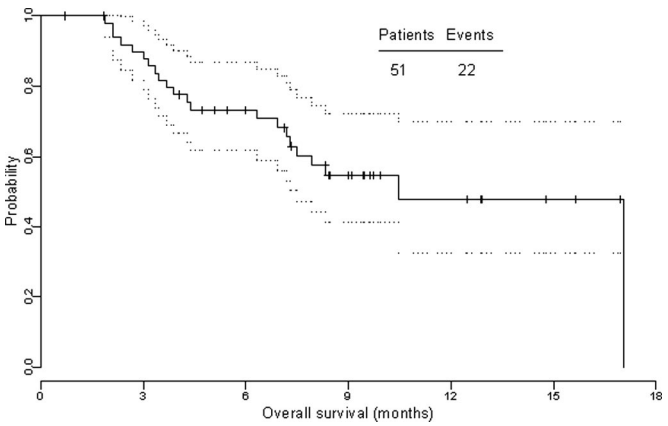

FIGURE 1. Overall survival. Probability of survival was estimated by the Kaplan/Meier method.

TABLE 3. Lung Cancer Symptom Scale questionnaire

	Total score[a]					
	Baseline	**End of cycle 1**	**End of cycle 2**	**End of cycle 3**	**End of cycle 4**	**End of cycle 5**
n	51	51	46	37	31	24
Mean ± SD	31.6 ± 19.1	28.8 ± 22.7	24.1 ± 19.5	24.0 ± 16.2	30.9 ± 24.6	25.4 ± 16.4
Median (range)	28.5 (2–72)	22.1 (3–100)	18.6 (0–73)	21.0 (3–70)	24.0 (3–100)	22.9 (4–58)

[a]Average of the aggregate score of all nine items was used for the total score. Repeated measure analysis considering time as continuous: $p = 0.29$. Repeated measure analysis considering time as discrete: $p = 0.52$.

TABLE 4. Worst NCI-CTC grade laboratory toxicities

		Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Hematology	Leucopenia	6	12	17	33	14	27	1	2
	Neutropenia	5	10	14	27	12	24	8	16
	Thrombocytopenia	5	10	3	6	3	6	1	2
	Anemia	11	22	23	45	9	18	0	0
Liver	Transaminase	5	11	1	2	0	0	0	0
	Bilirubin	-	-	4	9	0	0	0	0
Kidney	Creatinine	4	8	3	6	1	2	0	0

TABLE 5. Grade 3 or 4 NCI-CTC non-hematological toxicities

	Grade 3		**Grade 4**	
	n	**%**	**n**	**%**
Fatigue	6	12	—	—
Constipation	2	4	—	—
Anorexia	2	4	—	—
Peripheral neuropathy	2	4	1	2
Nausea	1	2	—	—
Stomatitis	1	2	—	—
Vomiting	1	2	—	—
Asthenia	1	2	—	—
Back pain	1	2	—	—
Urinary retention	1	2	—	—
Dyspnea	1	2	—	—

DISCUSSION

Among the different new anti-cancer agents that have been approved in NSCLC chemotherapy, paclitaxel, gemcitabine, vinorelbine, and docetaxel share a better efficacy/toxicity profile than older drugs. New drugs not only benefit younger patients, but also offer new treatment opportunities for the elderly. The benefit of chemotherapy for elderly patients with NSCLC has been proved in a multicenter controlled phase III study in which 191 patients older than 70 years with stage IIIB-IV NSCLC were randomized to vinorelbine or best supportive care.[19] Vinorelbine produced a 19.7% ORR and a longer median survival compared with best supportive care (27 versus 21 weeks, respectively). This survival benefit was corroborated by patient-reported outcomes in which QoL had concomitantly improved. In the recent Multicenter Italian Lung Cancer in the Elderly Study large phase III trial including 707 elderly patients with advanced NSCLC that compared single-agent chemotherapy using either gemcitabine or vinorelbine versus a doublet combination of both drugs, results showed no benefit in response rate, time to progression, survival, and QoL for the doublet combination.[20] The response rates of the single-drug chemotherapies or the non-platinum–based doublet chemotherapy regimens ranged from 15% to 22%, and the median survival times ranged from 18 to 36 weeks. Nevertheless, several recently published studies attempted to determine safety and activity of specific platinum and taxanes combinations in the elderly.[13,21] Until now, no randomized study has compared the efficacy and tolerability of standard platinum regimens with a single-drug regimen in elderly patients with NSCLC.

We designed this phase II trial to evaluate the safety and activity of a platinum-based doublet in elderly patients with advanced NSCLC. The combination of weekly paclitaxel plus monthly carboplatin was effective as first-line treatment with an ORR of 43%, median progression-free survival of 7.5 months, and median overall survival of 13.6 months. The lack of random allocation versus current standard chemotherapies for elderly patients (i.e., single-drug regimens) precluded a formal comparison with other schedules of chemotherapy. In addition, the survival results were given as a preliminary insight, as a longer follow up is needed. Nevertheless, these results are in the range of what could be expected for this disease, i.e., advanced and metastatic NSCLC, even in younger patients. Other studies evaluating patient populations with a younger median age who received a similar combination of weekly paclitaxel plus monthly carboplatin provided similar results.[13,22,23] In these phase II studies, paclitaxel 70 mg/m^2 given every week or 100 mg/m^2 given weeks 1, 2, and 3 was combined with carboplatin AUC 6 mg/ml^{-1}/min given day 1 of a 4-week schedule. ORRs ranged from 32% to 52%, and median survival ranged from 11 to 14 months.[13,22,23] As shown in Table 1, the study was conducted in a population with a median age of 74 years and ECOG PS 0 or 1 (only 10% of the patients had a PS of 2). Therefore, the results observed in this study mainly belong to a population of septuagenarian patients with good performance status.

Recently, two phase II studies investigated the efficacy of low-dose weekly carboplatin (AUC 2 mg/ml^{-1}/min) and

paclitaxel (50 or 80 mg/m^2) in elderly patients with advanced NSCLC.[24,25] Modest activity was observed in the Jatoi et al. study (n = 49) assessing paclitaxel 50 mg/m^2 with an ORR of 14%.[24] Better results were obtained in the Neubauer et al. study (n = 77) assessing paclitaxel 80 mg/m^2 with an ORR of 38%, a median progression-free survival of 3.5 months, and median survival of 7.2 months.[25]

As expected, the most common toxicity in this study was myelosuppression, with grade 3 or 4 neutropenia occurring in 39% of patients. However, grade 3 or 4 neutropenia was transient and of short duration, leading to only one episode of febrile neutropenia. Grade 3 or 4 thrombocytopenia occurred in few patients. Non-hematological toxicity related to study treatment was manageable with no unexpected adverse events in this elderly population. Grade 3 or 4 toxicity was infrequent; fatigue was the most common grade 3 adverse event. Grade 3 or 4 peripheral neurotoxicity occurred in three patients. Nevertheless, lower grade neurotoxicity would have been more appropriately evaluated using a neurophysiological examination and quantitative sensory testing. This method able to detect early paclitaxel-induced neuropathy was longitudinally evaluated in only one institution and could not be explored because of obvious subset bias.[26] Low-grade neuropathy is poorly evaluated in chemotherapy programs, although this long-lasting toxicity may affect QoL, particularly in elderly patients frequently affected by other neuropathy-induced comorbidities (e.g., diabetes mellitus, respiratory deficiency). The good safety profile of the paclitaxel-carboplatin combination in the elderly was also reported in a Cancer and Leukemia Group B randomized phase III study comparing paclitaxel alone versus this former doublet.[27] In this study, patients older than 70 years who had received the doublet regimen achieved a higher response rate and a longer progression-free survival than patients receiving paclitaxel alone.

Is the proposed weekly paclitaxel and monthly carboplatin schedule a progress in treatment of advanced NSCLC in the elderly? The present study cannot definitively answer to this question because of its phase II design. However, activity, safety profile, and QoL could be considered clues favoring the feasibility of this schedule in the elderly. What would be the comparator to be chosen in a further phase III design? Taking into account data regarding cisplatin-based chemotherapy, such as those described in the Kubota et al. study,[28] i.e., vindesine plus cisplatin or mitomycin, vindesine plus cisplatin, or etoposide plus cisplatin alternating with vindesine plus cisplatin, one can stress the fact that a classical cisplatin-based regimen encountered safety limitations in elderly patients. Studies specifically addressing the case of modern cisplatin-based doublets (cisplatin plus a third-generation drug) in the elderly are still lacking, and data obtained by subset analyses of patients older than 70 years in large randomized studies might be interpreted with caution as they include patients aged 70 to 75 years, rather than a general elderly population. Therefore, the current American Society of Clinical Oncology guidelines recommend the use of single-agent chemotherapy for elderly patients or patients with ECOG/Zubrod PS 2.[29] A single-drug regimen such as that validated in the ELVIS study[19] would probably be the best comparator to evaluate the role of weekly paclitaxel plus monthly carboplatin combination in elderly patients.

Because of the modest survival improvement induced by chemotherapy in advanced NSCLC, particularly in the elderly, patient-reported outcome, especially QoL, must be taken into account when evaluating a clinical benefit. In this study, the use of a lung cancer-specific QoL scale (LCSS) showed that the paclitaxel and carboplatin regimen could be administered with reasonable maintenance of QoL during therapy in elderly. However, these data must be cautiously interpreted: (a) the phase II nature of the study introduces a risk of overestimation of the QoL; (b) patient attrition from QoL evaluation along the chemotherapy program mainly affected those patients with poor response to therapy, patients who encountered adverse events, and/or patients for whom the disease progressed; and (c) patients lost to follow up from QoL evaluation are usually those with poorest QoL at baseline. In addition, it has been suggested that improved QoL results during phase II studies may be linked to either study agents or standard palliation and could cause overestimation of clinical benefit.[30]

The application of NSCLC guidelines[29] is a milestone in epidemiological observation and knowledge of the disease prognostic evolution. However, daily practice suggests that accounting for comorbidities in therapeutic decisions could be of paramount importance. Comorbid conditions are frequent in NSCLC patient populations, especially considering the high frequency of smokers in this population, and the comorbidity scores increase with age. Comorbidities are an important prognostic factor in patients with NSCLC and might therefore be included in the pretherapeutic evaluation in further studies.[31]

We conclude that only a phase III study with careful QoL assessment comparing two different approaches of chemotherapy; i.e., a single-drug regimen versus the platinum-based schedule described in this study, could determine whether this doublet regimen improved clinical benefit in the elderly patients with NSCLC. The weekly paclitaxel plus monthly carboplatin as an active regimen in elderly patients deserves further study to compare this approach versus the standard of care in this population.

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